Clinical Commissioning Policy
Mercaptamine hydrochloride viscous eyedrops for corneal cystine deposits in people aged 2 years and over (210503P) [1832]

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Commissioning position

Summary

Mercaptamine hydrochloride viscous eye drops are recommended to be available as a treatment option through routine commissioning for corneal cystine deposits within the criteria set out in this document.

Executive summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

About corneal cystine crystals

Cystinosis is a rare inherited disease caused by a genetic metabolic disorder where the build-up of a natural chemical called cystine causes damaging crystals to form in areas of the body such as the kidneys, most of the tissues of the eye, and in the muscles.

There are 3 different types of cystinosis: nephropathic infantile cystinosis (where symptoms first show in the kidneys and patients typically present under the age of 2 years); nephropathic juvenile cystinosis (similar symptoms but presenting in people older than 2 years); and non-nephropathic or ocular cystinosis (involving only crystals in the cornea of the eyes and mainly presenting in some teenagers and later in life).

All people with cystinosis have cystine crystals in their corneas (the transparent front part of the eye that covers the coloured part of the eye). If left untreated the cystine

crystals can cause symptoms such as light sensitivity, involuntary closure of the eye, eye pain or diseases of the eye surface. More severe complications such as reduced visual contrast sensitivity (the ability to distinguish between light versus dark; affected especially in situations of low light, fog or glare) can develop as the disease progresses. Complications from poorly managed corneal cystine crystals in older people can lead to permanent visual impairment or blindness.

About current treatments

The treatment currently available in the NHS for corneal cystine crystals is an unlicensed aqueous (water based) solution of mercaptamine hydrochloride, administered as eye drops.

About the new treatment

Mercaptamine hydrochloride (0.55%) viscous eye drops are licensed for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis. The viscous eye drops work the same way as the water-based formulations by reducing the build-up of cystine in the cornea, helping to reduce the volume and size of corneal crystals and improving symptoms. The gel formulation increases the amount of time the active ingredient has in contact with the eye. It also allows the dosing frequency to be reduced and the product to be stored at room temperature at which it remains stable for 7 days after first use.

What we have decided

NHS England has carefully reviewed the evidence prepared by NICE to treat corneal cystine crystals with viscous mercaptamine hydrochloride (0.55%) eye drops. We have concluded that there is enough evidence to consider making this treatment available.

Links and updates to other policies

This policy replaces the not routinely commissioned mercaptamine hydrochloride viscous eyedrops for corneal cystine deposits in people aged older than 2 years policy published in November 2020. (NHS England reference: 200807P)

Committee discussion

Clinical Panel considered that the evidence base was limited however it suggested the intervention was effective at reducing symptoms. Panel supported the proposition proceeding with a routine commissioning position.

See the committee papers (link) for full details of the evidence.

The condition

Cystinosis is a genetic metabolic disorder where the build-up of a natural chemical called cystine creates damaging crystals to form in areas of the body such as the kidneys and other areas of the body, including the muscles, pancreas, liver, thyroid gland and white blood cells. Crystals can also develop in most of the tissues of the eye, including conjunctiva, iris, retina and the cornea.

There are 3 types of cystinosis: infantile nephropathic cystinosis, juvenile nephropathic cystinosis and ocular (non-nephropathic) cystinosis. All people with cystinosis can have corneal cystine crystals and can develop symptoms such as photophobia (light sensitivity), blepharospasm (involuntary closure of the eye), eye pain and keratopathies (diseases of the eye surface).

More severe complications, such as increased glare disability, reduced visual contrast sensitivity (ability to distinguish between finer increments of light versus dark) and increased corneal thickness can develop as the disease progresses. Secondary glaucoma and visual impairment can develop with time. The long-term effects on the eye can include band keratopathy, punctate epithelial erosions and filamentary keratopathy (diseases of the eye surface); neovascularisation (the growth of blood vessels into the cornea which can interfere with vision) and iris abnormalities, such as posterior synechiae (where the iris adheres to the cornea and can lead to glaucoma) and iris thickening (Tsilou et al. 2002). Eye related complications can lead to blindness if left untreated.

Current treatments

The current treatment for corneal cystine crystals is an unlicensed formulation of aqueous mercaptamine hydrochloride (0.55%) eye drops which is produced under the terms of a `Specials` licence and is recommended to be applied 6 to 12 times per day (during waking hours).

New treatments

In January 2017 the European Medicines Agency (EMA) granted a marketing authorisation for mercaptamine hydrochloride (0.55%) viscous eye drops for the treatment of corneal cystine crystal deposits in adults and children from 2 years of age with cystinosis. The viscous eye drops use the same mode of action as the aqueous eye drop formulation, however, the added viscosity increases the amount of contact with the eye and allows the active ingredient to permeate the cornea. The new formulation increases the stability of the product which means the dosing frequency can be reduced and the eye drops can be stored in the refrigerator (2-8°C) before opening and at a controlled room temperature (up to 25°C) once opened, reducing the burden for patients and allowing for a better treatment response.

Epidemiology and needs assessment

The global incidence of cystinosis is estimated between 1 in 100,000 and 1 in 200,000 live births worldwide (Emma et al. 2014). Between 2 and 3 new cases of cystinosis are diagnosed in England each year. There are 159 patients (84 children and 75 adults) in England who are currently receiving treatment with systemic cysteamine to treat crystals in other areas of the body and use the aqueous eye drops to treat corneal cystine crystal deposits (Cystagon, Orphan Europe, internal data). In addition, 6 patients are registered with the Cystinosis Foundation UK (CF UK) with the rare form of ocular (non-nephropathic) cystinosis and currently use the aqueous eye drops only. This gives a total 165 people in England who potentially could be considered for treatment with mercaptamine hydrochloride (0.55%) viscous eye drops. Table 1 below shows a breakdown of patient numbers.

Table 1 Patient numbers

Estimates	Data Source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,000
Prevalence: 1/100,000 to 1/200,000 of live births	Orphanet	553 (low end of the range)
Diagnosed	Orphan Europe UK	220 (UK and Ireland)
Treated with systemic cystinosis treatment	Orphan Europe UK	208 (UK and Ireland) 159 England
Number of people registered with ocular cystinosis	Cystinosis Foundation UK	6 England
Number of people covered by licence in England (eligibility)	Combination of above sources	168 England

Evidence summary

NHS England has concluded that there is evidence to support a policy for the routine commissioning of this treatment for the indication.

The evidence on clinical effectiveness is based upon one phase III randomised controlled superiority trial with 31 people and a 90-day follow-up comparing viscous mercaptamine hydrochloride eye drops 0.55% (n=15) with aqueous mercaptamine hydrochloride eye drops 0.10% n=16; (Liang et al, 2017). This evidence is supported by a phase I/IIa single arm dose-response trial of viscous eye drops 0.55% involving 8 people over a 5 year-follow up (Labbé et al. 2014). Both were conducted in a French population and were open-label studies that recruited adults and children with nephropathic cystinosis and corneal cystine crystal deposits. Additional efficacy data for these studies was considered by the European Medicines Agency and provided in the European Public Assessment Report (EPAR).

Reduction in number of crystals

The primary outcome in both studies was the change in total number of corneal cystine crystal deposits (corneal cystine crystal density), in patient's eyes measured by in vivo confocal microscopy (IVCM - a laser imaging technique which examines the 7 corneal layers). Liang et al (2017) found that treatment with mercaptamine hydrochloride 0.55% viscous eye drops is associated with a statistically significant greater reduction of corneal cystine crystal deposits than mercaptamine hydrochloride 0.10% aqueous eye drops (40.4% and 0.7% respectively; p<0.0001). The EPAR reported there was a statistically significant estimated mean difference between treatment groups of 3.84 points [95% confidence intervals (CI) 2.11 to 5.56 points; p<0.0001)], indicating a benefit of reduced deposits for people receiving viscous eye drops. Assessments of corneal cystine deposits using both a slit-lamp and anterior-segment optical coherence tomography (AS-OCT) from measurements

of corneal cystine crystal scores (CCCS) also showed statistically significant reductions in corneal crystal density for people receiving viscous eye drops. Supporting evidence from Labbé et al. (2014) reported the mean IVCM score had reduced from baseline by 29.9% (SD 26.29) representing a statistically significant decrease (p=0.001) at 4 years follow-up and found the depth of deposits (based on CCCS and AS-OCT) also reduced over a 4-year period. This outcome suggests that people who use mercaptamine hydrochloride 0.55% viscous eye drops as a treatment for corneal cystine crystals in cystinosis can expect a statistically significant greater reduction in the number of crystals compared to treatment with mercaptamine hydrochloride 0.10% aqueous eye drops.

Maintenance of vision

Studies also assessed maintenance of vision by looking at ocular outcomes [including an assessment of visual acuity (clarity of vision) and visual contrast sensitivity (the ability to differentiate between certain shades of light versus dark colours)].

In the main study, (Liang et al. 2017), both visual acuity (assessed using a logMAR scale) and visual contrast sensitivity (assessed in log units) improved in both treatment groups at 90 days follow-up, visual acuity improved by a logMAR of -0.10 (SD 0.15) log units compared with an improvement of -0.07 (SD 0.15) log units, and visual contrast sensitivity improved by -0.20 (SD 0.27) log units compared with an improvement of -0.14 (SD 0.20) log units for people receiving viscous eye drops compared with aqueous eye drops respectively. Statistical significance was not reported. Labbé et al. (2014) reported best corrected visual acuity remained stable throughout the study period with a mean change in logMAR of 0.1 (SD 0.1) log units from baseline to 48 months (4 years) follow-up but did not report statistical significance. Changes in contrast sensitivity were not considered in Labbé et al. (2014). These results suggest that over a 90-day follow-up period of treatment with viscous mercaptamine hydrochloride 0.55% eye drops is at least as effective as treatment with aqueous mercaptamine hydrochloride 0.10% eye drops in maintaining visual acuity in people with corneal cystine crystal deposits, however statistical significance for this condition would only be demonstrated over several years. Normal vision was maintained over a 5 year period in a small cohort of 8 people.

Changes in symptoms

Changes in symptoms were assessed in both studies. In Liang et al. (2017), there was a statistically significant reduction in clinician assessed photophobia scores of -0.63 (SD 0.77) points for people receiving viscous eye drops compared with a small increase of 0.07 (SD 0.44) points for people receiving aqueous eye drops (p=0.0048). Additional evidence (reported in the EPAR), found patient reported mean photophobia scores decreased from baseline by -0.27 (SD 0.58) points at 90 days follow-up for people receiving viscous eye drops compared with a small increase of 0.23 (SD 0.72) points for people receiving aqueous eye drops, however statistical significance was not reported.

Labbé et al. (2014) also reported a decline in the mean clinician assessed photophobia scores from 2.8 (SD 1.1) points during the run-in period (while patients were receiving standard aqueous eye-drops regimen) to a mean score of 1.6 (SD

1.0) points at 60 months (5 years) follow-up, although they did not report statistical significance.

These results suggest that photophobia can continuously decrease over a 5-year follow–up as a result of treatment with viscous mercaptamine hydrochloride 0.55% eye drops and can result in a statistically significant greater reduction in photophobia over a 90-day follow-up in people with corneal cystine crystal deposits.

In Liang et al. (2017), corneal epithelial erosions, identified using a fluorescein dye corneal staining test (which helps detect corneal surface damage), reduced in both treatment groups at 90 days follow-up by -1.5 (SD 3.2) points versus -0.6 (SD 2.5) points (people receiving viscous eye drops versus aqueous eye drops respectively) although statistical significance was not reported. These results suggest there was no worsening of corneal staining in either treatment group during the 90 day follow-up period. Results of corneal staining were not reported in Labbé et al. (2014).

Changes in intraocular pressure (IOP), measured in millimetres of mercury (mm Hg) was used to assess pressure inside the eye. Results from Liang et al. (2017) found the mean measure of IOP recorded at 90 days follow-up was 15.0 (SD 3.2) mmHg for people receiving viscous eye drops compared with a mean value of 13.0 (SD 3.0) mm Hg in people receiving aqueous eye drops. Results from Labbé et al. (2014) found the mean IOP increased during the study period from 11.8 (SD 2.5) mm Hg at baseline to 14.8 (SD 2.3) mm Hg at 48 months (4 years follow-up). Results at 5 years (60 months) follow-up were not reported. These results suggest intraocular pressure changes varied and over a long-term follow-up showed increases but these remained within the normal range of IOP in healthy eyes (which is between 5 mm Hg and 22 mm Hg), and the increases could be explained by normal annual increases in children's IOP.

Patient reported pain at instillation

Pain when eye drops were administered was reported on a 0-100 mm visual analogue scale (VAS) and was reported in Labbé et al. (2014). At 30 days follow-up the mean pain-intensity VAS score was 27 (SD 19.7) mm higher for people treated with viscous eye drops compared with people receiving aqueous eye drops, which reported a mean score of 7.3 (SD 8.7) mm. During the 48 month follow-up period the reported pain at instillation decreased to less than 10 mm on the VAS at study end-point. The EPAR reported at 60 months (5 year) follow-up the mean VAS score was 7, although statistical significance was not reported.

Health related quality of life

Health related quality of life was assessed using the Comparison of Ophthalmic Medications for Tolerability (COMTol) questionnaire; a 37 item tool with 13 domains and 4 global questions which measures the extent to which any limitations in routine living activities (caused by side effects of topical eye treatment) interfere with health related quality of life, medication compliance, and patient satisfaction with their treatment. In Liang et al. (2017), 5 of the 7 adult patients receiving the viscous eye drops completed the COMTol questionnaire at baseline, 30 days follow-up and 90 days follow-up. Results at 90 days follow-up found that 2 patients were very satisfied, and 3 patients were somewhat satisfied with the viscous eye drops

treatment and all 5 patients indicated a preference for the viscous eye drops over their previous aqueous treatment.

Safety and tolerability

Safety was the main purpose of Labbé et al. (2014) but was also considered in Liang et al. (2017). In Labbé et al. (2014), 7 out of 8 patients reported 73 adverse events (AEs) of which 4 people (50%) reported severe AEs; 6 people (75%) reported serious AEs and 2 people (25%) reported drug-related AE and 1 person (12.5%) reported a treatment emergent AE at 5 years follow-up. There were no AEs reported as leading to discontinuation and no deaths. Local adverse drug reactions were also reported. Stinging was reported by 7 out of 8 people (87.5%) after eye drops were administered; 6 people (75%) reported blurred vision after eye drops were administered and 4 people (50%) reported burning or eye irritation after administration. The medium length of time for experiencing a local adverse drug reaction was 5 seconds. In Liang et al. (2017), 2 people in each treatment group reported serious AEs. There were no treatment emergent serious AEs in either treatment group and no severe AEs or deaths. Most of the local adverse drug reactions were described as mild or moderate in intensity (83.4%). More than 98% of the local adverse drug reactions at instillation lasted less than 1 hour. These results suggest treatment with viscous mercaptamine hydrochloride 0.55% eye drops were generally well-tolerated.

Evidence limitations

The main limitations with the evidence base are as follows:
Both Liang et al. (2017) and Labbé et al. (2014) were conducted in a population with nephropathic cystinosis. Although Liang et al. (2017) reported that 38.7% of people completing the study were adults, the mean ages of both populations (17.1 years in Liang et al. 2017 and 12.1 years in Labbé et al. 2014) means there is limited evidence representing older age groups and for the sub-types with juvenile nephropathic cystinosis or non-nephropathic cystinosis.
However, this should not impact the ability to generalise to non-nephropathic and older people.

The strength of concentration (0.10%) of the aqueous formulation comparator used in Liang et al. (2017) does not represent the current standard of care in England (which is a 0.55% concentration), and the EPAR noted that the comparator is generally recommended to be applied every hour while awake rather than the 4 times per day dose used during the study; however, in practice, hourly administration is not usually maintained.

There are some questions surrounding the methods used in the studies. In Labbé et al. (2014), it is unclear if clinician assessed photophobia scores were made by masked assessors and this therefore has some cause for potential bias. In addition, the baseline data from Liang et al. (2017) showed people receiving viscous eye drops had a higher mean baseline corneal staining reading than those receiving aqueous eye drops. Although the statistical significance of the baseline reading was not reported, it is not clear how this may have influenced follow-up results.

There is limited evidence of health-related quality of life. The COMTol questionnaire was only completed by 5 adults in Liang et al. (2017) and therefore it is difficult to generalise findings.

Liang et al. (2017) had a short-term follow-up of 90 days, providing limited efficacy and safety analysis. Data from un-controlled settings provides support for longer term efficacy and safety. Longer term data is available from Labbé et al. (2014; up to 5-year follow-up), but this involved a small sample of 8 patients and therefore it is difficult to generalise findings.

Implementation

Criteria

Patient eligibility:

Mercaptamine hydrochloride (0.55%) viscous eye drops will be commissioned when the following conditions are met:
People aged 2 years or over with a confirmed diagnosis of infantile or juvenile nephropathic cystinosis OR non-nephropathic (ocular) cystinosis, and who have corneal cystine crystal deposits

AND

Confirmed nephropathic cystinosis
Leukocyte cystine levels (LCL) greater than 0.3 nmol cystine per mg protein and clinical presentation with Fanconi syndrome with or without genetic analysis of *CTNS* gene

OR

Confirmed ocular cystinosis
Corneal cystine crystals visible under slit lamp examination or in vivo confocal microscopy (IVCM) and clinical presentation without Fanconi syndrome with or without genetic analysis of CTNS gene.

Confirmation of corneal cystine crystals is based on:

Presence of corneal crystals based on an assessment by a paediatric or adult ophthalmologist with experience in diagnosing corneal cystine crystals (the assessment should include the front part of the eye, grading of crystals, and a full ocular examination including the retina and optic nerve).

Initiation of treatment

For people diagnosed with cystinosis affecting the kidneys and eyes; viscous mercaptamine hydrochloride (0.55%) eye drops should be started by a consultant nephrologist based at a specialist cystinosis centre in consultation with a consultant ophthalmologist. Ongoing follow up will need to be by both teams.

For people diagnosed with ocular cystinosis without kidney involvement; viscous mercaptamine hydrochloride (0.55%) eye drops should be started and followed up by a consultant ophthalmologist based at a specialist cystinosis centre.

According to the summary of product characteristics, the recommended dose is one drop in each eye, 4 times a day during waking hours. The recommended interval between each instillation is 4 hours. The dose can be decreased progressively (to a minimum total daily dose of 1 drop in each eye) depending on the results of ophthalmic examination (such as corneal cystine crystal deposits, photophobia). One vial should only be used for 7 days after opening.

Where patients are likely to be allergic to or have reacted to the preservatives contained within this product a preservative free product should be prescribed.

Assessment of benefit

Patients receiving mercaptamine hydrochloride (0.55%) eye drops should receive regular follow-up assessments by consultant ophthalmologist at a specialist cystinosis centre.

Mercaptamine hydrochloride (0.55%) eye drops should be continued where clinical benefit is evident based on results of ophthalmic examination (reduction of corneal crystals, including maintenance of low levels of corneal crystals or no presence of corneal crystals; reduction of symptoms such as photophobia and corneal irregularities; treatment is well-tolerated; patient reports satisfaction with treatment). Although no effects during pregnancy and breast-feeding are anticipated, precautions should be taken with concomitant treatment with oral mercaptamine and viscous eye drops. Mercaptamine should not be used during pregnancy, particularly during the first trimester, unless clearly necessary (summary of product characteristics).

Patients who are pregnant or planning to become pregnant should be advised of the possibility of toxicity and disruption to the developing foetus if they are using concomitant oral cysteamine.

Patients receiving concomitant oral cysteamine should not breastfeed.

Stopping criteria:

Mercaptamine hydrochloride (0.55%) viscous eye drops will be discontinued if:

- Patient experiences no clinical benefit (based upon crystal build-up) upon annual clinical assessment
- Patient experiences treatment emergent adverse effects
- Patient is unable to tolerate local adverse drug reactions (for example eye irritation, burning or stinging).

Patient pathway

Nephropathic cystinosis

Following a clinical suspicion of nephropathic cystinosis as a consequence of symptoms of Fanconi syndrome in young people aged 2 years and older (based on the marketing authorisation), patients are usually referred to a specialist cystinosis centre for confirmatory diagnosis. Cystinosis is usually diagnosed by a nephrologist who refers the patient to an ophthalmologist to carry out an ophthalmic assessment

and record symptoms of photophobia or watery eyes. Visual assessments involve an assessment of visual acuity (using Snellen or logMAR charts or other age appropriate sight test), and detection of corneal and conjunctival crystals on slit lamp examination (using hand held slit-lamp in very young children) (Biswas et al. 2018).

Patients will receive the oral cysteamine capsules for non-ocular symptoms and are currently offered treatment with aqueous eye drops for ocular symptoms. Treatment is usually overseen by a consultant nephrologist but patients may also receive follow-up appointments by other medical specialists, including ophthalmologists, neurologists, endocrinologists, clinical geneticists, as well as specialist nurses (Cystinosis Foundation, UK).

Ocular cystinosis (non-nephropathic)

For people who have ocular cystinosis, diagnosis generally takes place in teenage years or adulthood when corneal crystals have developed. An optometrist may see visible signs of corneal cystine crystals during an eye examination and will refer the patient to an ophthalmologist for an ophthalmic assessment (including visual assessments of visual acuity (using Snellen or logMAR charts), and detection and quantification of crystals (based on slit-lamp assessments and using corneal cystine crystal score grading [Gahl score]). Use of in-vivo confocal microscopy of the cornea and imaging the front of the eye with anterior segment optical coherence tomography may be useful adjuncts for quantitative assessment of corneal crystal load pre-treatment and post-treatment).

Treatment

Once crystals are identified, treatment should start immediately in line with licence and may be provided by a multidisciplinary team (MDT) including an endocrinologist, nephrologist, and an ophthalmologist. Treatment is provided by a consultant nephrologist or consultant ophthalmologist based in a specialist cystinosis centre.

Review

Frequency of the follow-up appointments depends on the clinical status of the patient and is therefore variable but is at a minimum on a 6-month basis.

Governance arrangements

<u>For people with nephropathic cystinosis:</u>
Patients with nephropathic cystinosis with suspected corneal cystine crystals will be diagnosed by a specialist cystinosis centre and will be assessed within 6 weeks of diagnosis by an ophthalmologist for an initial ocular assessment.

Prescription and monitoring of patients should be overseen by an ophthalmologist with experience in managing cystinosis, however patients will be monitored and assessed by a nephrologist who will be responsible for prescribing treatment with mercaptamine hydrochloride (0.55%) viscous eye drops and providing patient information regarding storage of the eye drops, usage, and side-effects.

For people with non-nephropathic (ocular) cystinosis:
Patients will be diagnosed with corneal cystine crystals by carrying out an ocular assessment.

Ocular assessments will be carried out by an ophthalmologist with experience in corneal disease who will also be responsible for prescribing and monitoring treatment with mercaptamine hydrochloride (0.55%) viscous eye drops and providing patient information regarding storage of the eye drops, usage, and side-effects. All patients will receive ocular assessments at 6-month basis.

Each provider organisation treating children with a medicine approved under this policy will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place. Provider organisations must register all patients using software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Proposed governance arrangements should be in line with the arrangements set out by the relevant NHS England standard contracts for cystinosis (all ages).

Mechanism for funding

The funding of mercaptamine hydrochloride will be managed through the relevant NHS England Regional Specialised Commissioning Team. Blueteq forms will be completed to support audit of this policy.

Audit requirements

For people with nephropathic cystinosis, data regarding treatment monitoring and compliance it is intended to make this accessible through the National Registry of Rare Kidney Diseases (RaDaR), (once agreed).

Data for people with non-nephropathic (ocular) cystinosis will be gathered at their regular outpatient ophthalmologist assessments.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Cystinosis	A rare inherited disease caused by a mutation to the CTNS gene (which encodes the protein cystine) and produces the build-up of cystine crystals in the human body
Cystine	A natural chemical (amino acid) which is found in proteins in the body
Cysteamine (also known as mercaptamine)	A medicine which reduces the build-up of cystine in areas of the body and reduces symptoms caused by cystinosis
Instillation	Administration of a liquid drop by drop
European public assessment report (EPAR)	The published report which explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the studies performed, to reach their recommendations on how to use the medicine
European Medicines Agency (EMA)	The agency which evaluates medicinal products for use in the European Union
In vivo confocal microscopy (IVCM)	A non-invasive laser imaging technique which examines the 7 different layers of the cornea
Anterior segment optical coherence tomography (AS-OCT)	An imaging technique used to analyse the depth of corneal cystine crystal deposits and central corneal thickness in the front of the eye
Corneal cystine crystal score (CCCS) Also known as a Gahl score	A grading scale to identify the density of corneal cystine crystals ranging from 0.00 (showing clarity in the centre of the cornea) to 3.00 (showing greatest crystal density)
Specials licence	Special-order unlicensed medicines which are made to meet the needs of an individual patient. They have not been assessed for safety, quality or efficacy by the relevant licensing authorities and the prescriber carries all legal responsibility.

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